Bactericidal activity of moxifloxacin against *Staphylococcus aureus*

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Moxifloxacin, an 8-methoxyfluoroquinolone, has enhanced activity against Gram-positive organisms in comparison with other quinolones [1,2]. This spectrum of activity, together with its favorable pharmacokinetic properties [3], have prompted interest in its use in the oral treatment of deep-seated and problematic infections such as infective endocarditis (IE) and osteomyelitis, infections which might otherwise require extended courses of intravenous antibiotics. However, bacterial killing rather than mere inhibition may be an important determinant of success in these infections. The inhibitory activity of moxifloxacin has been investigated previously in comparison with other agents for a number of bacterial species [4–6]. Moreover, time-kill studies suggest that the agent is bactericidal against *Staphylococcus aureus* [7], but relatively few laboratory and clinical strains have been investigated. Accordingly we have determined the minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) of moxifloxacin for a range of clinical isolates of *S. aureus*. For comparison, ciprofloxacin MICs and MBCs were determined simultaneously.

Thirty-nine strains of *S. aureus* were investigated, of which 21 were isolated as the causal organism from patients with IE, and the remainder were miscellaneous clinical isolates responsible for infection or colonization. All strains were isolated in this laboratory. Active surveillance of both community- and hospital-acquired infections is in place in this hospital, and to our knowledge the isolates were epidemiologically unrelated. MICs and MBCs were determined by tube inoculation using the method in routine use in this laboratory [8]. The Oxford *Staphylococcus* (NCTC 6571) was included as a control with each batch of tests. Briefly, isolates were cultured in liquid medium to log phase, then inoculated under controlled conditions into Brain Heart Infusion broth containing doubling dilutions of ciprofloxacin or moxifloxacin in appropriate ranges with the aim of exceeding 5×10^5 CFU/mL. The inoculum was counted using standard methods and the tubes incubated at 37 °C with mixing at 20 and 24 h, when the MIC was the lowest concentration of antibiotic which had inhibited visible turbidity of the medium. Surviving bacteria were enumerated at 24 h by subculturing a volume of 0.02 mL on solid medium, and spreading to reduce the effects of antibiotic carry-over. The MBC was the lowest concentration of antibiotic which had reduced the viable count by a factor of 1000 (3-log kill) compared to the original inoculum, after a further 24 h incubation.

With the exception of a single strain, ciprofloxacin MICs were bimodally distributed in the ranges 0.5–2 mg/L and 64–128 mg/L (Table 1). Many of the ciprofloxacin-resistant strains were also resistant to methicillin, reflecting the fact that the methicillin-resistant *S. aureus* (MRSA) strains in this region are often resistant to both agents. Ciprofloxacin MBCs were never more than fourfold higher than the corresponding MICs (ranges 0.5–4 mg/L and 64–512 mg/L).

Moxifloxacin MICs correlated with those of ciprofloxacin but were 8–64-fold lower, with ranges of 0.03–0.125 mg/L for the ciprofloxacin-sensitive group and 2–8 mg/L for the ciprofloxacin-resistant group. These data are compatible with previous reports [5].

Corresponding moxifloxacin MBCs were 0.06–0.25 mg/L in the ciprofloxacin-sensitive group, and 2–8 mg/L in the ciprofloxacin-resistant group. As with ciprofloxacin, for no strain was the MBC of moxifloxacin more than four times greater than the MIC.

The treatment of deep-seated infections can be both difficult and controversial, and is frequently influenced as much by the practicalities of intravenous administration and patient compliance as by clinical guidelines. For instance, for patients allergic to penicillin, the treatment currently recommended in the UK for staphylococcal endocarditis comprises intravenous vancomycin and gentamicin [9]. This regimen necessitates in-patient management and frequent therapeutic monitoring, and may be nephrotoxic. There is therefore mounting interest in the potential of oral agents in such circumstances, either singly or in combination.

Moxifloxacin is a recently developed 8-methoxyfluoroquinolone which has high bioavailability when administered by mouth, is well tolerated and has a prolonged serum half-life permitting once- or twice-daily administration [7]. Its enhanced activity, particularly against Gram-positive organisms, has led to interest in its use against infections such as endocarditis

Table 1 MICs and MBCs of ciprofloxacin and moxifloxacin

Number	Site	Ciprofloxacin MIC (mg/L)	MBC (mg/L)	Moxifloxacin MIC (mg/L)	MBC (mg/L)
1	IE	0.5	0.5	0.03	0.06
2	IE	1	1	0.03	0.06
3	IE	1	1	0.03	0.06
4	IE	0.5	0.5	0.06	0.06
5	IE	0.5	0.5	0.06	0.06
6	IE	1	2	0.06	0.06
7	IE	0.5	0.5	0.03	0.125
8	IE	0.5	0.5	0.06	0.125
9	IE	1	1	0.06	0.125
10	IE	1	1	0.06	0.125
11	IE	0.5	1	0.06	0.125
12	IE	0.5	1	0.06	0.125
13	IE	0.5	1	0.06	0.125
14	IE	0.5	1	0.06	0.125
15	IE	1	2	0.06	0.125
16	IE	2	2	0.06	0.125
17	IE	0.5	2	0.06	0.125
18	Blood	1	2	0.06	0.125
19	Sputum	1	2	0.06	0.125
20	Wound	1	2	0.06	0.125
21	Wound	2	2	0.06	0.125
22	IE	2	4	0.06	0.125
23	IE	2	4	0.125	0.125
24	IE	1	1	0.06	0.25
25	Sputum	8	16	0.25	0.5
26	Nose	64	128	2	2
27[a]	Nose	64	128	2	2
28[a]	Wound	64	256	2	2
29[a]	Empyema	64	256	2	2
30[a]	Wound	64	256	2	2
31[a]	Sputum	64	256	2	2
32	Nose	64	64	2	4
33[a]	Wound	128	128	2	4
34[a]	Nose	64	256	2	4
35[a]	Urine	64	256	2	4
36[a]	Wound	128	256	2	4
37	Blood	128	256	4	4
38[a]	IE	128	512	4	4
39[a]	Wound	128	512	8	8

[a]Denotes strain resistant to methicillin (MRSA).

and osteomyelitis. Although its advantages in such situations are speculative, this unit has favorable experience of the use of oral moxifloxacin for the treatment of a case of complicated staphylococcal endocarditis of the mitral valve (strain 17, Table 1). This infection failed to respond to conventional treatment with high-dose intravenous flucloxacillin and fusidic acid, but the addition of oral moxifloxacin was curative.

The importance of bactericidal, as opposed to inhibitory, activity in the successful treatment of deep-seated infections has been much debated. Although recent guidelines have recommended the abandonment of routine MBC measurement in such cases [9], it seems reasonable where data are available to favor bactericidal over bacteriostatic antibiotics in these circumstances [10]. Accordingly we have investigated the bactericidal activity of moxifloxacin against endocarditic and other clinical strains of *S. aureus*.

The results reported here demonstrate that moxifloxacin is both inhibitory (MIC ≤ 0.125 mg/L) and bactericidal (MBC ≤ 0.25 mg/L) against strains of *S. aureus* with ciprofloxacin MICs below 2 mg/L. These values are well within the levels reached following standard oral doses [3], and are in accord with the tentative proposal that staphylococci with moxifloxacin MICs

below 2 mg/L be regarded as sensitive [11]. Moxifloxacin is less active against strains that are more resistant to ciprofloxacin, but the MICs and MBCs remain close to attainable serum levels. It should be cautioned, however, that the use of moxifloxacin against organisms with borderline MICs might lead to the promotion of greater degrees of resistance, both to moxifloxacin and to other quinolones.

In summary, it is clear that among sensitive strains of *S. aureus*, moxifloxacin is bactericidal at clinically achievable levels. These observations support the potential of moxifloxacin in the treatment of deep-seated infections caused by ciprofloxacin-sensitive strains of *S. aureus*.

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